REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

In the Official Action under reply, the Examiner indicated that Claims 1-3 and 5-26 were present in the application. This was not correct. As is clear from the Listing of Claims and the Remarks in applicant's August 15, 2003 Reply and Amendment, Claims 1-3 and 5-51 were in the application at the time of issuance of the November 4, 2003 Official Action. The November 4, 2003 Official Action is therefore not an Action on the merits of Claims 27-51, which have apparently been overlooked by the Examiner.

Claims 1-3, 5, 6, 10-31 and 35-51 are now in this application. Claims 7-9 and 32-34 are canceled, without prejudice or disclaimer, and Claims 10, 11, 35 and 36 are amended by the present amendment. Claim 4 was canceled previously. Claims 1, 5, 6, 27-31 and 37-51 remain as previously presented in the August 15, 2003 amendment, while Claims 2, 3 and 12-26 remain as originally filed.

The Examiner's previous acknowledgment of applicant's Information Disclosure Statements and return of the Examiner-initialed copy of applicant's Forms PTO-1449 are again noted, with appreciation. With the previous Official Action, Applicant received initialed copies of Sheets 1, 3, 4 and 5 of the five-sheet Form PTO-1449 filed January 17, 2002 and Sheet 1 of 1 of the Form PTO-1449 filed May 8, 2002. It is again requested that an initialed copy of Sheet 2 of the Form PTO-1449 filed January 17, 2002, be provided with the next official communication.

A further copy of Sheet 2 of that Form PTO-1449 is enclosed for the Examiner's convenience.

As noted in applicant's August 15, 2003 Reply and Amendment, the present application claims benefit of U.S. Provisional Application No. 60/224,358, filed August 11, 2000. See paragraph [0001] of the specification. It is again requested that the Examiner acknowledge this claim for domestic priority under 35 U.S.C. § 119(e) in the next official communication.

Claims 1-3 and 5-26 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement because the specification purportedly does not support the phrase "but not having macular edema", which is considered to be new matter. Applicant strongly disagrees with the Examiner and submits that all of the claims now in this application are supported by the as-filed specification.

In applicant's previous response, it was pointed out that the original specification clearly discloses retinopathies that are not associated with macular edema as well as those which are; therefore, applicant is not introducing new matter by placing this limitation in his claims. Applicant continues to submit that the as-filed specification supports this limitation and that the original specification describes the invention in such a way that one of ordinary skill in the art would understand that the present invention enabled treatment of retinopathy in a mammal not having macular edema at the time the application was filed.

Applicant does not deny that his specification describes retinopathies which are known to be associated with macular edema as well as retinopathies that are known to be unassociated with macular edema, that is, retinopathies in patients not

having macular edema. Applicant originally described his invention as including all kinds of retinopathies. However, it is well-settled in patent law that an applicant should not be prevented from claiming his patentable subject matter simply because he learned after filing that he was not the first to invent the broad genus. Applicant is now claiming less than the full scope of the disclosure. However, as the predecessor of the C.A.F.C., the C.C.P.A., succinctly stated in *In re Wertheim*, 191 U.S.P.Q. 90, 97:

> Inventions are constantly made which turn out not to be patentable, and applicants frequently discover during the course of prosecution that only a part of what they invented and originally claimed is patentable.

It is then for the applicant to determine the bounds of protection that he will seek. In doing so, form should not be allowed to triumph over substance, so that an applicant cannot retreat to otherwise patentable subject matter simply because he erroneously thought he were first with the genus when he filed. In the case *In re Johnson and Farnham*, 194 U.S.P.Q. 187, a case which is in point, the C.C.P.A. stated:

> The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species therein, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of §112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute.

The C.C.P.A. went on to state that the specification, having described the whole, necessarily also described the part remaining. Appellants in that case merely excised the invention of another, to which they were not entitled; they did not create an artificial subgenus or claim new matter. A copy of the *In re Johnson and Farnham* decision is appended hereto.

On pages 4-8 of his specification, applicant discloses a number of kinds of retinopathies which his invention seeks to treat; he discloses all phases of diabetic retinopathy, including non-proliferative diabetic retinopathy, diabetic macular edema, preproliferative and proliferative diabetic retinopathy, including preventing (slowing the progression of) diabetic retinopathy in patients not yet having diabetic retinopathy; he also discloses retinopathies known as branch retinal vein occlusion, sickle cell retinopathy, retinopathy of prematurity and central retinal vein occlusion. Applicant also describes in the specification a clinical study of diabetics using carbonic anhydrase inhibitors where the patients at the beginning of study period had either no retinopathy or nonproliferative retinopathy and over a period of two years, showed no progression of retinopathy overall. None of these patients had macular edema. (Note the description of the various stages of diabetic retinopathy defined on page 14 of the specification in the discussion of the CAI GROUP and the NON-CAI GROUP.) The rate of progression in the patients not treated with carbonic anhydrase inhibitors was much quicker.

The question thus is whether applicant's teaching in his specification of all of these types of retinopathies teaches one skilled in the art use of his invention in the treatment of retinopathies in subjects not having macular edema. It is submitted that the answer must be affirmative, based on what was known in the field of retinopathy at the time of applicant's invention. Provided herewith are copies of a number of publications in this field which predate applicant's application and which conclusively shows that there are retinopathies described by applicant which are accompanied by macular edema and there are retinopathies described by applicant which are not accompanied by macular edema. Since prior workers (in art previously cited herein)

treated macular edema, including macular edema associated with diabetic retinopathy, using carbonic anhydrase inhibitors, such treatment would presumably inherently treat the diabetic retinopathy associated with the macular edema, and applicant no longer claims such treatment. However, as the publications submitted herewith, and listed on the accompanying Form PTO-1449 for the Examiner's convenience, conclusively demonstrate, there are many patients suffering from diabetic retinopathy who do not have macular edema; these publications also show that there are patients having other types of retinopathies who also do not have macular edema. It is clear from these publications that it was known at the time of applicant's invention that many patients having retinopathy do not have macular edema. It is also clear from the instant specification, that applicant did indeed describe treating retinopathies in patients not having macular edema, because applicant specifically described treating numerous retinopathies which were known at the time of his invention to not be associated with macular edema.

Turning to the actual publications presented herewith to prove applicant's point, which are numbered [1] through [14] on the enclosed Form PTO-1449, and which are referred to by those same numbers below, the following remarks summarize what was known about the association of macular edema with retinopathy at the time of applicant's invention:

While macular edema may occur in diabetic retinopathy, this is true for only a minority of patients. In an extensive study of the Icelandic diabetic population Kristinsson [1-3] found that 9.3% of type I diabetics had or had history of macular edema. The group of diabetics who had had the disease for less than 20 years had only a 1.6% prevalence of macular edema. The 4-year incidence of macular edema

was found to be 3.4%. This compares to 8.2% in a group of diabetics in Wisconsin [4].

In type II diabetes, Kristinsson [1-3] found the prevalence of macular edema to be 10% overall, 8.8% in the group with type II diabetes for <20 years and 15% in the group with diabetes for 20 years or more. Lower prevalence numbers were found by Klein [5] in Wisconsin 3.7%, Klein et al [6] in Beaver Dam in Wisconsin 0.7%, and a similar number was found by Sparrow et al [6] in Melton Mowbray in England, 10%. These papers confirm the widely-accepted fact that only a relatively small minority of diabetics suffers from macular edema while a large majority has retinopathy.

In the studies in Iceland by Kristinsson et al [1-3], the prevalence of any retinopathy in type I diabetics was 52%, going up to 86% in those with more than 20 years duration of disease. In type II diabetes, the overall prevalence of retinopathy was 40% which is similar to the findings by Klein in Wisconsin (38%) [5], in Sweden 43% [7], in Denmark 45% [8], in Taiwan 3.5% [9] and in Beaver Dam Wisconsin 30% [6] as well as in Melton Mowbray England 52% [10].

At any given time less than 10% of diabetics have macular edema and in some studies this number is much lower, all the way down to 0.7% of the diabetic population. At the same time, most studies show a prevalence of retinopathy of at least around 40% in type II and 50% in type I and this increases with a duration of retinopathy to reach 80-100% after about 30 years duration of diabetes of either type [1]. Thus, there are many diabetic patients with diabetic retinopathy or at risk of developing diabetic retinopathy who do not have macular edema.

The present patent addresses the treatment of diabetic retinopathy in the early stages, including non-proliferative and preproliferative retinopathies. For the first 10 years after diagnosis of diabetes mellitus of type I macular edema is extremely rare and in the study of the Icelandic diabetic population, not a single case was found of macular edema in this patient-group [1]. The aim of the patent is to treat the large majority (90%+) of diabetics who do not have diabetic macular edema but who still have or are at risk of developing sight-threatening retinopathy.

Retinopathy of prematurity is not associated with macular edema. These patients have peripheral neovascularization, bleeding and traction detachments of the retina but do not have macular edema. A Medline search associating macular edema and retinopathy of prematurity reveals no references to this point. This is confirmed in Duane's Clinical Ophthalmology on CD ROM 2002 edition; see the enclosed copy of the chapter of Duane's by J.A. McNamara and W. Tasman relating to retinopathy of prematurity [11]. See also pages 332-334 of [12], another ophthalmology text. There is no mention of macular edema in the detailed descriptions of retinopathy of prematurity in these texts.

Macular edema is not a component of sickle cell disease. Macular edema has never been reported in association with sickle cell retinopathy and this can be confirmed in standard textbooks in ophthalmology, for example Duane's Clinical Ophthalmology on CD ROM 2002 edition, copy of the chapter on sickle cell disease by Donald A Gagliano, Lee M Jampol and Maurice F. Rabb enclosed [13]. See also pages 330-331 of [12], the Kanski ophthalmology text.

Unlike diabetic retinopathy, macular edema is frequently seen in branch retinal vein occlusion and is the most common cause of vision loss and need for

treatment in this disease. Patients having the retinopathy known as branch retinal vein occlusion thus ordinarily have macular edema and therefore their treatments would not be encompassed by the present claims.

Central retinal vein occlusion is a type of retinopathy usually associated with edema of the retina. Treatment of such patients therefore would not be within the scope of the present claims.

Both branch retinal vein occlusion and central retinal vein occlusion are discussed in the enclosed chapter from Duane's Clinical Ophthalmology by George E. Sanborn, Larry E. Magargal and Edward A. Jaeger [14].

The fact that carbonic anhydrase inhibitors have previously been suggested for treating macular edema in no way suggests that such treatment could be extended to retinopathies in patients who do not have macular edema. There are many patients suffering from retinopathies who do not have macular edema, including the large majority of diabetics, patients with retinopathy of prematurity and patients with sickle cell retinopathy. This is evident from the publications provided herewith and cited above. The instant specification clearly teaches treatment of these patients; it thus clearly teaches treating retinopathy in a mammal in need of such treatment but not having macular edema. It is clear from the publications provided herewith that it was well-known at the time of applicant's invention that many retinopathies, including most diabetic retinopathies, are not associated with macular edema. Such are clearly taught by applicant to be treatable in accord with his invention. Moreover, a simple well-known method can be used to determine if any given patient has or does not have macular edema. Thus, any question about

whether a retinopathy patient has macular edema can be answered by any ophthalmologist.

The diagnosis of diabetic macular edema is a basic part of ophthalmology and can be found in any textbook. The diagnosis may be made through an ophthalmologist's slit lamp examination of the fundus with dilated pupils with the aid of a indirect ophthalmoscopy lens (60-90 diopters) or less frequently with a corneal contact lens (Goldmann lens) or even less commonly with a Hruby lens in front of the cornea. The ophthalmologist visualizes the thickening of the retina in the macular area and thus makes the diagnosis. This can be done in any ophthalmologist's office or clinic. Secondly, the diagnosis of macular edema can be documented with stereoscopic fundus photographs. Thirdly, fluorescein angiography is useful in further diagnosing and verifying fluorescein leakage which accompanies diabetic macular edema. All three of these methods have been in use for a long time. (OCT, optical coherence tomography, is a fairly new method to measure the thickening of the retina and is a very good way to diagnose and measure diabetic macular edema.)

In view of the foregoing, it is clear that one skilled in the art would reasonably conclude from applicant's specification that applicant had possession of the invention now claimed at the time the application was filed. Further, applicant's specification clearly enables one skilled in the art to practice the invention as now claimed without undue experimentation. The fact that applicant's specification enables more than he now claims does not detract from the fact that he clearly enables treatment of retinopathies in patients not having macular edema. The Examiner is urged to not allow form to triumph over substance here but rather to allow applicant to retreat to

that portion of his originally disclosed subject matter which is new, useful and unobvious. Withdrawal of the rejection under 35 U.S.C. § 112 first paragraph, and allowance of all of the claims are believed to be in order and are earnestly solicited.

Respectfully submitted,

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